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Office for Research Subjects

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Division of Dockets Management (HFA-305)
Attention Nancy L. Stanisic
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Request for Comments on FDA Rules for Reporting Adverse Events in Clinical Trials

Dear Dr. Stanisic:

We appreciate the opportunity to provide written comments on how the effectiveness and efficiency of the reporting and review of adverse events by IRBs might be improved. The Human Research Protection Program (HRPP) of this school has recently given considerable thought to this issue and has, as a result, extensively revised its policy on reporting of adverse events and unanticipated problems. Copies of our revised policy and reporting form are attached.

The specific comments that follow are organized as suggested in your recent announcement of the public hearing and solicitation of written comment.

1. Role of the IRBs

The role of the IRBs is to ensure that the rights and wellbeing of research subjects are protected to the greatest extent possible before, during and after their participation in research. This role includes a responsibility to ensure competent review of adverse events and other problems that arise during research when these are unanticipated, reasonably related to the conduct of the study, and involve risk to study subjects or others. Furthermore, the IRBs must ensure that, following review, appropriate actions are taken to protect subjects. In our view, however, these responsibilities are best met by the joint efforts of the IRB and the data monitoring mechanism that is reviewed and approved by the IRB before the trial is initiated, e.g., data and safety monitor, DSMB, etc. In this arrangement, the IRBs are responsible for prompt review of events that may require immediate action to protect subjects and for ensuring that the safety monitoring mechanism is fully competent to review, analyze and act upon, or recommend action upon, aggregated reports of expected AEs and SAEs.

2. Types of reportable adverse events

The IRBs should only receive for review reports of events upon which they can and should act, or consider acting, to protect subject rights and wellbeing. These include reports of all individual events for studies that the IRB has approved and that are unanticipated (not described in the study protocol, investigator's brochure or consent form), reasonably related to the conduct of the study, and cause risk to subjects or others. AEs or SAEs that are anticipated should only be reported when they are more serious than anticipated or occur more frequently than anticipated (this latter category can only be determined when aggregated data are decoded and analyzed by the DSMB). Deaths should be reported, unless the investigators are confident these are due to the natural progression of the subject's underlying condition, and this has been predefined in the approved study protocol.

What should not be reported to IRBs are (i) AEs and SAEs that are anticipated, or other events, e.g. possible AEs/SAEs , the significance of which can only be determined when aggregated data are decoded and analyzed, (ii) reports from other sites in a multi-site study for which the IRB is not responsible, and (iii) reports from other studies in which use of the drug or device differs from that in the approved study. It is our opinion that these are the tasks of the DSMB/Safety Monitor, which has the study code, the appropriate statistical expertise and the responsibility to review study safety data at whatever interval it considers most appropriate. The DSMB must, however, provide regular reports of its reviews to the IRB.

In addition to the above, we suspect that AEs are under-reported by researchers carrying out behavioral intervention studies because it is not clear to them how AEs, as typically defined, apply to their studies. In our view, this reflects the orientation of FDA exclusively toward clinical trials of drugs or devices. While that may be reasonable, given the FDA focus on clinical trials of drugs and devices, IRBs that review such non-clinical trials find little explicit guidance in either HHS or FDA regulations that can assist the IRB's effort to develop policies on AEs that can be applied to non-clinical research.

3. Practices of reporting adverse events to IRBs

Current HHS regulations do not address the reporting of "adverse events" and that term does not appear in HHS policies and guidelines. However, HHS and FDA both address "unanticipated problems involving risks to subjects or others". Whatever the final determination by FDA regarding adverse event reporting, we would urge that FDA and HHS regulations should employ a single integrated scheme of terminology and definitions that encompasses AEs, SAEs and unanticipated problems and that can be used by IRBs as they review the full range of studies for which they are responsible.

Sponsors and DSMBs should provide IRBs with sufficient timely information from interim data analyses so that the IRB is fully informed in its deliberations concerning stopping of studies, revising consent documents, or requiring other changes to protect research subjects.

The FDA defines an adverse event as any untoward medical occurrence that may present itself during treatment with, or administration of, a pharmaceutical product or medical device, and which may or may not have a causal relationship with the treatment. We view this definition as being directed more to sponsor reporting requirements than to investigators. IRBs are left to independently define the meaning for researchers. Lack of a clear, consistent definition of what must be reported causes confusion among researchers and IRBs. As a result, researchers conducting clinical research over-report AEs to IRBs in order to comply with the AE reporting requirements of funding agencies, and pharmaceutical sponsors, and sometimes the IRBs themselves. As noted above, such reports are typically uninterpretable by IRBs because they do not hold the assignment code for the trial.

We hope these comments are of help in your deliberations on this important issue.

Sincerely,

Nathaniel F. Pierce
Institutional Official
Human Research Protection Program